

PATENT SPECIFICATION

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(54) ORAL COMPOSITIONS CONTAINING TRIFLUOROMETHYL PHENYL BIS-BIGUANIDES AS ANTIPLAQUE AGENTS

(71) We, THE PROCTER & GAMBLE COMPANY, a corporation organised and existing under the laws of the State of Ohio, United States of America, of 301 East Sixth Street, Cincinnati, Ohio 45202, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to oral compositions such as toothpastes and mouthwashes containing certain trifluoromethylphenyl bis-biguanides having excellent antiplaque performance and reduced tendency to stain the teeth.

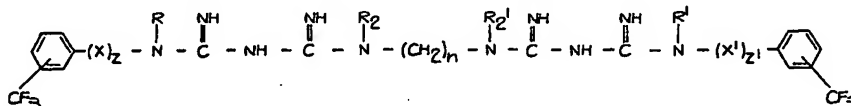
The field of this invention is "oral compositions" which term is used herein to designate products which in the ordinary course of usage are retained in the oral cavity for a time and in a manner sufficient to contact essentially all of the dental surfaces, but are not intentionally ingested. Such products include, for example, dentifrices, mouthwashes, prophylaxis pastes and topical solutions.

The bis-biguanide and antibacterial agents such as chlorhexidine, 1,6 bis (N⁵-p-chlorophenyl-N¹-biguanido) hexane, are known to be effective antiplaque agents, but it has been recognised that they have a tendency to produce severe staining of the teeth. Belgian Patent 801,703 discloses the use of the insoluble salts of the bis-biguanides in oral compositions as a means of reducing the stain problem. Belgian Patent 811,878 and Specification No. 1,507,846 disclose the use of metal ion chelator compounds, such as amino acids, aminopolycarboxylates and hydroxypyrones, with the bis-biguanides to reduce stain. DTOS (German Published Specification) No. 2,627,548 discloses certain bis-biguanides, wherein the bridging alkylene group has from 1 to 4 carbon atoms instead of six, which have substantially lower staining tendencies than chlorhexidine.

Description of the Invention

It has now been discovered that certain novel bis-biguanide compounds wherein the bridging alkylene group is C₁ to C₄ alkylene, and wherein the terminal nitrogen atoms contain trifluoromethylphenyl groups, have outstanding antiplaque activity and very low tendency to stain the teeth.

The novel bis-biguanide compounds of this invention have the generic formula



wherein n is from 1 to 4 inclusive (preferably 2 to 4 inclusive); wherein X and X' each represent an alkylene radical containing from 1 to 3 carbon atoms, wherein z and z' each can be either 0 or 1; wherein R and R', each represent either hydrogen,

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an alkyl radical containing from 1 to 12 carbon atoms, or an aralkyl radical containing from 7 to 12 carbon atoms and wherein R_2 and R_2' each represent either hydrogen or an alkyl radical of 1 to 2 carbon atoms. Preferred is the compound wherein z and z' are each 0, n is 2 and R , R' , R_2 and R_2' are hydrogen. Preferably, the trifluoromethyl group is in the meta position; however, the corresponding ortho and para-isomers are also suitable for use herein. The pharmaceutically acceptable salts of the foregoing compounds are especially desirable. The water soluble salts, especially the dihydrochloride, digluconate and diacetate salts, are the most desirable since they make possible the formation of clear solution compositions. In contrast with chlorhexidine, whose dihydrochloride salt is insoluble in water, the hydrochlorides of the compounds of the present invention are water-soluble. Typically, the hydrochloride salt is inherently formed in the preparation of chlorhexidine and of the compounds of the present invention. For purposes of this application, water-soluble salts are considered to be those having a solubility of greater than about 0.04% by weight in water at 25°C.

Examples of bis-biguanidines falling within the scope of the present invention are the following:

Bis(N^5 -*m*-trifluoromethylphenyl- N^1 -biguanidino)methane,
1,2-bis(N^5 -*m*-trifluoromethylphenyl- N^1 -biguanidino)ethane,
1,4-bis(N^5 -*m*-trifluoromethylphenyl- N^1 -biguanido)butane,
1,2-bis(N^5 -*m*-trifluoromethylbenzyl- N^1 -biguanido)ethane,
1,2-bis(N^5 -*p*-trifluoromethylphenyl- N^1 -biguanido)ethane,
1,2-bis(N^5 -*o*-trifluoromethylphenyl- N^1 -biguanido)ethane,
1,2-bis(N^5 -*m*-trifluoromethylphenyl- N^5 -hexyl- N^1 -biguanido)ethane,
1,2-bis(N^5 -*m*-trifluoromethylphenyl- N^5 -2-phenethyl- N^1 -biguanido)ethane,
1,2-bis(N^5 -*m*-trifluoromethylphenyl- N^1 -ethyl- N^1 -biguanido)ethane,
1,4-bis(N^5 -*m*-trifluoromethylphenyl- N^5 -ethyl- N^1 -methyl- N^1 -biguanido)butane,
1,2-bis(N^5 -*m*-trifluoromethyl- N^5 -methyl- N^1 -ethyl- N^1 -biguanido)ethane,

and their water soluble salts, for example, the digluconate, dihydrochloride and diacetate salts. The most preferred compounds are 1,2-bis(N^5 -*m*-trifluoromethylphenyl- N^1 -biguanido)ethane and its dihydrochloride, diacetate and digluconate salts.

The compounds of the invention can be made by reacting ethylene or methylene diamine dihydrochloride (or an appropriately N,N' substituted ethylene or methylene diamine dihydrochloride) or a homologue thereof with sodium dicyanamide to give, for example, a bis (N^3 -cyano- N^1 -guanidino)ethane, which is then reacted with the hydrochloride of the desired *m*-trifluoromethyl phenylamine or other isomer to give the desired bis-biguanide compound in the form of its hydrochloride salt. The general preparation procedure for bis-biguanides is well known in the art; see, for example, Warner et al. J. Pharm. Sci. 62 No. 7, 1189-91 (1973) and Rose et al. J. Chem. Soc. 4422 (1956).

The novel bis-biguanide antiplaque agents of the present invention are utilized in oral hygiene in the form of oral compositions which comprise from 0.01% to 2.5% (preferably from 0.05% to 1.2%, and most preferably from 0.1% to 0.8%) by weight of the bis-biguanide antiplaque agent and the balance, a carrier suitable for use in the oral cavity. All percentages herein are by weight, unless specified otherwise. Depending upon the composition, lesser or greater amounts may be used. In general, all that is required is to have an effective amount of the bis-biguanide compound in the mouth sufficient to give antiplaque and/or anticaries effectiveness. Generally, an amount of 0.001 grams or more per usage of the bis-biguanide can be considered as an effective amount for plaque control.

The pH of the compositions of this invention is preferably maintained within the range of from 4.5 to 9.5. Below 4.5, damage to dental enamel can occur. Above 9.5, the alkalinity becomes cosmetically undesirable and may irritate soft tissue in the mouth.

As previously stated, compositions of the present invention comprise the afore-described bis-biguanide antiplaque agents and a carrier suitable for use in the oral cavity. The carrier can be water or an organic solvent such as alcohol. Preferably, however, the carrier portion of the oral composition is a conventional preparation such as a toothpaste, mouthwash or chewing gum.

Dentifrices contain an abrasive polishing material and typically also contain sudsing agents, flavoring and sweetening agents. Toothpastes usually additionally contain humectants and binders and water. The dentifrices herein comprise from 0.5% to 95% abrasive in addition to the bis-biguanide antiplaque agent.

Any abrasive polishing material which does not excessively abrade dentin can be used in these dentifrice compositions. These include, for example, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, calcium polymetaphosphate and insoluble sodium polymetaphosphate. Preferably, however, the abrasive is one which has a high degree of compatibility with the bis-biguanide. These include, for example, condensation products of urea and formaldehyde such as disclosed by Cooley et al. in U.S. Patent 3,070,510, granted December 25, 1962, silica xerogels such as those disclosed in U.S. Patent 3,538,230 to Pader et al., issued November 3, 1970, hydrofluoric acid-treated amorphous silica abrasives such as those disclosed in U.S. Patent 3,862,307 to DiGiulio, issued January 21, 1975, and mineral abrasives coated with cationic polymers such as those disclosed in British Patent 1,506,045. The abrasives generally have a particle size of from 0.1 to 20 microns in diameter.

The total amount of abrasive materials in the dentifrice embodiments of this invention can range from 0.5% to 95% by weight of the dentifrice. Preferably, toothpastes contain from 6% to 60%, and toothpowders contain from 20% to 95% abrasives.

Dentifrices usually contain surface-active agents (also called sudsing agents).

Suitable surface-active agents are those which are reasonably stable and form suds throughout a wide pH range, and which will not react with the bis-biguanide compound, i.e., nonsoap nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents.

The nonionic synthetic detergents which can be used with the oral compositions of the present invention may be broadly defined as compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound which may be aliphatic or alkyl-aromatic in nature. The length of the hydrophilic or polyoxyalkylene radical which is condensed with any particular hydrophobic group can be readily adjusted to yield a water-soluble compound having the desired degree of balance between hydrophilic and hydrophobic elements.

For example, a well-known class of nonionic synthetic detergents is made available on the market under the trade name of "Pluronic". These compounds are formed by condensing ethylene oxide with a hydrophobic base formed by the condensation of propylene oxide with propylene glycol. The hydrophobic portion of the molecule which, of course, exhibits water insolubility has a molecular weight of from 1,500 to 1,800. The addition of polyoxyethylene radicals to this hydrophobic portion tends to increase the water solubility of the molecule as a whole and the liquid character of the products is retained up to the point where polyoxyethylene content is about 50% of the total weight of the condensation product.

Other suitable nonionic synthetic detergents include:

1. The polyethylene oxide condensates of alkyl phenols, e.g., the condensation products of alkyl phenols having an alkyl group containing from 6 to 12 carbon atoms in either a straight chain or branched chain configuration, with ethylene oxide, the said ethylene oxide being present in amounts equal to 10 to 60 moles of ethylene oxide per mole of alkyl phenol. The alkyl substituent in such compounds may be derived from polymerized propylene, diisobutylene, octane, or nonane, for example.

2. Those derived from the condensation of ethylene oxide with the product resulting from the reaction of propylene oxide and ethylene diamine—products which may be varied in composition depending upon the balance between the hydrophobic and hydrophilic elements which is desired. For example, compounds containing from 40% to 80% polyoxyethylene by weight and having a molecular weight of from 5,000 to 11,000 resulting from the reaction of ethylene oxide groups with a hydrophobic base constituted of the reaction product of ethylene diamine and excess propylene oxide, said base having a molecular weight of the order of 2,500 to 3,000, are satisfactory.

3. The condensation product of aliphatic alcohols having from 8 to 18 carbon atoms, in either straight chain or branched chain configuration, with ethylene oxide, e.g., a coconut alcohol ethylene oxide condensate having from 10 to 30 moles of ethylene oxide per mole of coconut alcohol, the coconut alcohol fraction having from 10 to 14 carbon atoms.

4. Long chain tertiary amine oxides corresponding to the following general formula:



wherein R_1 contains an alkyl, alkenyl or monohydroxy alkyl radical of from 8 to 18 carbon atoms from 0 to 10 ethylene oxide moieties, and from 0 to 1 glyceryl moiety, and R_2 and R_3 contain from 1 to 3 carbon atoms and from 0 to 1 hydroxy group,

e.g., methyl, ethyl, propyl, hydroxy ethyl, or hydroxy propyl radicals. The arrow in the formula is a conventional representation of a semi-polar bond. Examples of amine oxides suitable for use in this invention include dimethyldodecylamine oxide, oleyldi-(2-hydroxyethyl)amine oxide, dimethyloctylamine oxide, dimethyldecylamine oxide, dimethyltetradecylamine oxide, 3,6,9-trioxaheptacyldiethylamine oxide, di(2-hydroxyethyl)tetradecylamine oxide, 2-dodecoxyethyl dimethylamine oxide, 3-dodecoxy-2-hydroxypropyldi(3-hydroxypropyl)amine oxide, and dimethyl hexadecylamine oxide.

5. Long chain tertiary phosphine oxides corresponding to the following general formula



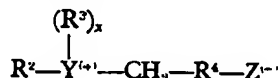
wherein R contains an alkyl, alkenyl or monohydroxyalkyl radical ranging from 8 to 18 carbon atoms in chain length, from 0 to 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety and R' and R'' are each alkyl or monohydroxyalkyl groups containing from 1 to 3 carbon atoms. The arrow in the formula is a conventional representation of a semi-polar bond. Examples of suitable phosphine oxides are:

dodecyldimethylphosphine oxide,
 tetradecyldimethylphosphine oxide,
 tetradecylmethylethylphosphine oxide,
 3,6,9-trioxaoctacyldimethylphosphine oxide,
 cetyldimethylphosphine oxide,
 3-dodecoxy-2-hydroxypropyldi(2-hydroxyethyl)phosphine oxide,
 stearyldimethylphosphine oxide,
 cetylethylpropylphosphine oxide,
 oleyldiethylphosphine oxide,
 dodecyldiethylphosphine oxide,
 tetradecyldiethylphosphine oxide,
 dodecyldipropylphosphine oxide,
 dodecyldi(hydroxymethyl)phosphine oxide,
 dodecyldi(2-hydroxyethyl)phosphine oxide,
 tetradecylmethyl-2-hydroxypropylphosphine oxide,
 oleyldimethylphosphine oxide, and
 2-hydroxydodecyldimethylphosphine oxide.

6. Long chain dialkyl sulfoxides containing one short chain alkyl or hydroxy alkyl radical of 1 to 3 carbon atoms (usually methyl) and one long hydrophobic chain which contains alkyl, alkenyl, hydroxy alkyl, or keto alkyl radicals containing from 8 to 20 carbon atoms, from 0 to 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety. Examples include:

octadecyl methyl sulfoxide,
 2-ketotridecyl methyl sulfoxide,
 3,6,9-trioxaoctadecyl 2-hydroxyethyl sulfoxide,
 dodecyl methyl sulfoxide,
 oleyl 3-hydroxy propyl sulfoxide,
 tetradecyl methyl sulfoxide,
 3-methoxytridecyl methyl sulfoxide,
 3-hydroxytridecyl methyl sulfoxide, and
 3-hydroxy-4-dodecoxybutyl methyl sulfoxide.

The zwitterionic synthetic detergents useful in the oral compositions of the present invention can be broadly described as derivatives of aliphatic quaternary ammonium, phosphonium, and sulfonium compounds, in which the aliphatic radicals can be straight chain or branched, and wherein one of the aliphatic substituents contains from 8 to 18 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. A general formula for these compounds is:



wherein R² contains an alkyl, alkenyl, or hydroxy alkyl radical of from 8 to 18 carbon atoms, from 0 to 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety; Y is selected from the group consisting of nitrogen, phosphorus, and sulfur atoms; R³ is

an alkyl or monohydroxyalkyl group containing 1 to 3 carbon atoms; x is 1 when Y is a sulfur atom and 2 when Y is a nitrogen or phosphorus atom, R⁴ is an alkylene or hydroxyalkylene of from 1 to 4 carbon atoms and Z is a radical selected from the group consisting of carboxylate, sulfonate, sulfate, phosphonate, and phosphate groups.

Examples include:

- 4 - [N,N - di(2 - hydroxyethyl) - N - octadecylammonio] - butane - 1 - carboxylate;
- 5 - [S - 3 - hydroxypropyl - S - hexadecylsulfonio] - 3 - hydroxypentane - 1 - sulfate;
- 10 3 - [P,P - diethyl - P - 3,6,9 - trioxatetradecoxylphosphonio] - 2 - hydroxypropane - 1 - phosphate;
- 3 - [N,N - dipropyl - N - 3 - dodecoxy - 2 - hydroxypropylammonio] - propane - 1 - phosphonate;
- 15 3 - (N,N - dimethyl - N - hexadecylammonio)propane - 1 - sulfonate;
- 3 - (N,N - dimethyl - N - hexadecylammonio) - 2 - hydroxypropane - 1 - sulfonate;
- 4 - [N,N - di(2 - hydroxyethyl) - N - (2 - hydroxydodecyl)ammonio] - butane - 1 - carboxylate;
- 20 3 - [S - ethyl - S - (3 - dodecoxy - 2 - hydroxypropyl)sulfonio] - propane - 1 - phosphate;
- 3 - [P,P - dimethyl - P - dodecylphosphonio] - propane - 1 - phosphonate; and
- 5 - [N,N - di(3 - hydroxypropyl) - N - hexadecylammonio]2 - hydroxypentane - 1 - sulfate.

The cationic synthetic detergents useful in the oral compositions of the present invention can be broadly defined as quaternary ammonium compounds having one long alkyl chain containing from 8 to 18 carbon atoms such as lauryl trimethylammonium chloride; cetyl pyridinium chloride; cetyl trimethylammonium bromide; di-isobutylphenoxyethyl dimethylbenzylammonium chloride; coconutalkyltrimethylammonium nitrite; and cetyl pyridinium fluoride. Especially preferred are the quaternary ammonium fluorides described in Briner et al, U.S. Patent 3,535,421, issued October 20, 1970, where said quaternary ammonium fluorides have detergent properties.

The amphoteric synthetic detergents useful in the present invention can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight chain or branched and wherein one of the aliphatic substituents contains from 8 to 18 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxylate, sulfonate, sulfate, phosphate, or phosphonate. Examples of compounds falling within this definition are sodium 3-dodecylamino propionate, sodium 3-dodecylaminopropane sulfonate, dodecyl-beta-alanine, N-alkyltaurines such as the one prepared by reacting dodecylamine with sodium isothionate according to the teaching of Kosmin, U.S. Patent No. 2,658,072, issued November 3, 1973, N-higher alkyl aspartic acids such as those produced according to the teaching of Lynch, U.S. Patent No. 2,438,091, issued November 16, 1948, and the products sold under the trade name "Miranol" and described in Mannheimer, U.S. Patent No. 2,528,378 issued October 31, 1950.

Many additional nonionic, cationic, zwitterionic and amphoteric synthetic detergents are known to the art and can be used as sudsing agents in the compositions herein. Further examples can be found in *McCutcheon's Detergents and Emulsifiers, 1972 Annual*, published by Allure Publishing Corporation.

The sudsing agent can be employed at levels ranging from 0.5 to 5.0% of the dentifrice composition.

Dentifrices normally also contain flavoring agents. Suitable flavoring agents for use in the dentifrices herein include, for example, wintergreen oil (methyl salicylate), oil of peppermint, oil of sassafras (synthetic), and oil of anise. Flavoring agents are present at a level of from 0.01% to 2.0%.

Dentifrices normally also contain sweetening agents. Suitable sweetening agents for use in dentifrices include, for example, saccharin, dextrose and levulose. The sweetening agents are used at levels of from .05% to 2%.

In toothpastes it is desirable to employ thickening agents such as hydroxyethylcellulose and water-soluble salts of cellulose ethers, including sodium carboxymethyl cellulose and sodium carboxymethylhydroxyethyl cellulose; or natural gums, including gum karaya, gum arabic and gum tragacanth. Also, colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to improve

the texture of the product. Thickening agents are used at levels of from 0.1% to 5.0% of the toothpaste composition.

It is also desirable to include a humectant material in toothpastes. Suitable materials for this purpose include glycerine, sorbitol, and other edible polyhydric alcohols or mixtures thereof. These materials can comprise from 1% to 50% of the toothpaste composition. In addition to the aforementioned typical components of a toothpaste, water usually comprises the balance of the toothpaste, and is usually present at levels up to 50%.

Mouthwashes generally comprise a water/ethyl alcohol solution and optionally other ingredients such as flavor, sweeteners, and humectants such as those mentioned above for dentifrices. The alcohol provides an antibacterial effect. Optionally, mouthwashes also contain sudsing agents such as those mentioned above for dentifrices. Humectants such as glycerine and sorbitol give a moist feel in the mouth and are desirably also present. Antibacterial agents are sometimes incorporated into mouthwashes (or dentifrices) at levels from .01% to 2.0%.

Generally, mouthwashes suitable for use as carriers herein contain 5% to 40% ethyl alcohol, 0% to 20% (preferably 5% to 20%) glycerine or other humectants, 0% to 2% (preferably 0.1% to 2%) sudsing agent, 0% to 0.5% (preferably 0.05% to 0.5%) sweetening agent such as saccharin and 0% to 0.3% (preferably 0.05% to 0.3%) flavoring agent, and the balance, water.

Chewing gum suitable for use as a carrier herein comprises a gum base and flavoring materials such as those mentioned above for dentifrices. The flavoring materials are present at a level of 0.01% to 2.0% of the final chewing gum composition. The gum base is a chewable plastic gum material such as natural rubber, chicle, polyvinyl acetate, ester gum, coumarone resin, and paraffin wax. The gum base is typically made from a mixture of two or more plastic gum materials to achieve a preferred degree of plasticity for chewing. Optionally, corn syrup is added as a softener and binder for the chewing gum and sugar is optionally added as a filler and sweetener. A typical chewing gum suitable as a carrier herein comprises 15% to 30% gum base, 15% to 20% corn syrup, 50% to 65% sugar, and 0.05 to 1.5% flavoring materials.

Lozenges suitable as carriers herein comprise a hard sugar candy base and one or more flavoring materials. The flavoring materials are present at levels between 0.01% and 2.0%. Optionally, lozenges can contain various other materials. A typical lozenge suitable as a carrier in this invention is a hard candy comprised of a hard candy base containing 0.05% to 1.5% flavor. The hard candy base is a solidified solution of amorphous sugar which is generally formed from a sugar solution which has been cooked at high temperature so as to remove nearly all of the moisture. The flavoring materials and antiplaque agent are added before the moisture is removed. The flavoring materials mentioned hereinbefore for dentifrices are also exemplary of those suitable for use in lozenges.

When formulating the antiplaque agents of the present invention into an oral composition, the amount which is incorporated into the composition should be sufficient to provide at least 0.001 grams of antiplaque agent per usage of the composition. Thus, in dentifrices, where the amount of product used per usage is from 1 to 4 grams, the amount of antiplaque agent in the dentifrice should be at least 0.03%, preferably from 0.1% to 2%, and most preferably from 0.5% to 1.5%. In mouthwashes, typical usage is from about 10 to 20 grams, and the amount of antiplaque agent in the mouthwash should be at least 0.01, preferably from 0.5% to 1.5%, and most preferably from 0.1% to 1.0%.

Typical usage of chewing gum and lozenges is from about 1 to 4 grams and the amount of antiplaque agent in the chewing gum or lozenge should be at least 0.03%, preferably from 0.1% to 2%, and most preferably from 0.5% to 1.5%.

Generally, oral compositions should contain from 0.01% to 2.5% of the antiplaque agent.

The oral compositions of the present invention can also optionally contain additional therapeutic materials for use in the oral cavity such as anticaries agents, (e.g., water-soluble fluoride such as sodium fluoride and stannous fluoride) and anticalculus agents such as trisodium ethane 1-hydroxy-1,1 diphosphonate.

Although the novel bis-biguanide compounds of the present invention give considerably less staining of the teeth than chlorhexidine, they are not completely free of staining potential and it is, therefore, often desirable to include in the compositions of the invention certain chelating agents which are useful in combating the general tendency of bis-biguanide antiplaque agents to stain the teeth, as well as the tendency of the teeth to become stained from natural causes such as contact with certain foods

and beverages. Such chelating agents are disclosed in Haeefe, U.S. Patent 3,937,807, issued February 10, 1976; and in Specification No. 1,507,846. Examples of chelating agents useful for this purpose are nitrilo-triacetic acid, ethylenediamine diacetic acid, kojic acid, maltol, ethyl maltol, calcium dihydrogen ethylenediamine tetraacetate, and di-N-substituted ethylene diamine diacetic acids wherein the substituents can be ethyl or 2-hydroxyethyl. The pharmaceutically acceptable water-soluble salts of these chelators are particularly useful, e.g., the sodium, potassium and ammonium salts. When a chelator is used, enough chelator should be present in the compositions such that some excess chelator is present in addition to that which reacts or would react with the bis-biguanide present. The concentration of such excess chelator generally ranges from 0.01% to 1.25% by weight of the composition. Generally, two moles of chelator react with one mole of bis-biguanide compound.

This invention will be further illustrated by the following examples:

EXAMPLE I

A toothpaste is prepared according to the following formula:

Component	Parts by weight
Sorbitol (70% soln.)	20.00
Sodium saccharin	0.21
Veegum (colloidal magnesium aluminum silicate)	0.40
Precipitated urea/formaldehyde condensate (abrasive)	30.00
Flavor	1.00
Sodium carboxymethylcellulose	1.30
Glycerine	10.00
1,2 - bis(N ⁶ - m - bifluoromethylphenyl - N' - biguanido) - ethane digluconate	0.70
Polyoxyethylene sorbitan (20) monoisostearate	1.50
Distilled water	balance to 100

This tooth paste, when used in the normal manner, is effective in retarding the formation of dental plaque and produces an appreciably lower level of stain on the teeth than does chlorhexidine.

EXAMPLE II

A mouthwash in accordance with the present invention is formulated as follows:

Component	Parts by weight
Ethyl alcohol (95% in water)	12.00
Cetyl pyridinium chloride	0.10
Polyoxyethylene (20) sorbitan monooleate	0.12
Sodium hydroxide (10% in water)	0.02
Sodium saccharin	0.055
Flavoring	0.16
1,2 - bis(N ⁶ - m - trifluoromethylphenyl - N' - biguanido)ethane dihydrochloride	0.20
Color	0.50
Sorbitol (70% in water)	12.00
Distilled water	balance to 100

When used in the normal manner to rinse the mouth, this product is effective in retarding the formation of dental plaque and produces an appreciably lower level of stain on the teeth than does chlorhexidine.

EXAMPLE III

A chewing gum in accordance with the present invention is formulated as follows:

	Component	Parts by weight	
	Gum base	21.30	
5	Ester Gum	6.40	5
	Coumarone resin	9.60	
	Dry latex rubber	3.20	
	Paraffin wax (M.P. 180°F.)	2.10	
	Sugar	58.45	
10	Corn syrup (Baume 45)	18.20	10
	Flavoring	1.05	
	1,2 - bis(N ⁵ - m - trifluoromethylphenyl - N ¹ - biguanido)ethane diacetate	1.00	

Chewing this gum in the normal manner retards the formulation of dental plaque and produces appreciably less staining of the teeth than does chlorhexidine.

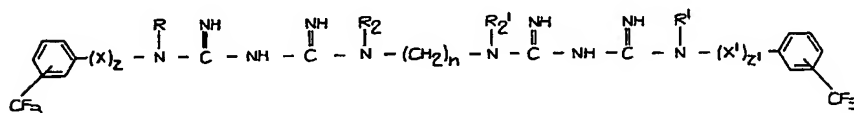
EXAMPLE IV

When in the preceding examples the 1,2 - bis(N⁵ - m - trifluoromethylphenyl - N¹ - biguanido)ethane salts are replaced by the digluconate or diacetate salts of the following compounds, similar results are obtained in that antiplaque performance is obtained with appreciably less staining to the teeth than is obtained if chlorhexidine is used:

- 1,4 - bis(N⁵ - m - trifluoromethylphenyl - N¹ - biguanido)butane,
 1,2 - bis(N⁵ - m - trifluoromethylbenzyl - N¹ - biguanido)ethane,
 1,2 - bis(N⁵ - m - trifluoromethylphenyl - N⁶ - hexyl - N¹ - biguanido)ethane,
 1,2 - bis(N⁵ - m - trifluoromethylphenyl - N⁶ - 2 - phenethyl - N¹ - biguanido)ethane,
 1,4 - bis(N⁵ - m - trifluoromethylphenyl - N⁶ - ethyl - N¹ - methyl - N¹ - biguanido)butane,
 1,2 - bis(N⁵ - m - trifluoromethylbenzyl - N⁵ - methyl - N¹ - biguanido)ethane,
 1,2 - bis(N⁵ - m - trifluoromethylphenyl - N⁵ - phenethyl - N¹ - biguanido)ethane,
 1,2 - bis(N⁵ - p - trifluoromethylphenyl - N¹ - biguanido)ethane,
 1,2 - bis(N⁵ - o - trifluoromethylphenyl - N¹ - biguanido)ethane, and
 Bis - (N⁵ - m - trifluoromethylphenyl - N¹ - biguanido)methane.

WHAT WE CLAIM IS:—

1. A bis-biguanide compound having the generic formula:



wherein n is from 1 to 4 inclusive; X and X' each represent an alkylene radical containing from 1 to 3 carbon atoms; z and z' are each 0 or 1; R and R' are each hydrogen, an alkyl radical containing from 1 to 12 carbon atoms or an aralkyl radical containing from 7 to 12 carbon atoms; and R₂ and R₂' are each hydrogen or an alkyl radical of 1 to 2 carbon atoms; and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein the salt is a water-soluble salt.
 3. A compound according to claim 1 or 2 wherein the salt is dihydrochloride diacetate or digluconate salt.
 4. A compound according to any one of claims 1 to 3 wherein n equals 2, z and z' are each 0 and R, R', R₂ and R₂' are each hydrogen.
 5. A compound according to any one of claims 1 to 4 wherein the trifluoromethyl groups are in the meta position.
 6. A bis-biguanide compound or a pharmaceutically acceptable salt thereof substantially as hereinbefore described in the Examples.
 7. An oral composition comprising a carrier suitable for use in the oral cavity and from 0.01% to 2.5% by weight of composition of an antiplaque agent consisting of a bis-biguanide compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6.

8. A composition according to claim 7 wherein the amount of antiplaque agent in the composition is from 0.05% to 1.2% by weight of the composition.

9. A composition according to claim 7 wherein the amount of antiplaque agent in the composition is from 0.1% to 2.0% by weight of the composition and the composition contains as an additional ingredient from 0.5% to 95% by weight of the composition of an abrasive.

10. A composition according to claim 7 in the form of a mouthwash wherein the antiplaque agent is present at a level of from 0.5% to 1.5% by weight of the composition and wherein the composition contains as additional components:

A. from 5% to 40% ethyl alcohol;

B. from 0% to 20% humectant;

C. from 0% to 2% sudsing agent;

D. from 0% to 0.5% sweetening agent;

E. from 0.05% to 0.3% flavouring agent; and

F. water.

11. A composition according to any one of claims 7 to 10 which additionally contains from 0.01% to 1.25% by weight of the composition of a chelator in excess of the amount of chelator which will react with the bis-biguanide compound, said chelator being nitrilotriacetic acid, ethylenediamine diacetic acid, kojic acid, maltol, ethyl maltol, calcium dihydrogen ethylenediamine tetraacetate, a di-N-substituted ethylene diamine diacetic acid wherein the substituents are ethyl or 2-hydroxyethyl, and the pharmaceutically acceptable water-soluble salts of said chelators.

12. A composition according to claim 7 substantially as hereinbefore described in the Examples.

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